34. The set of reagent pairs of claim 33 wherein said antibody binding compound is a monoclonal antibody or a polyclonal antibody, and wherein k is in the range of from 1 to 3.

35. The set of reagent pairs according to claims 30, 31, 32, 33, or 34 wherein said second antibody binding compound is a monoclonal antibody or a polyclonal antibody, and wherein said active species is singlet oxygen or hydrogen peroxide.

36. The set of reagent pairs of claim 35 wherein said sensitizer is capable of generating singlet oxygen when photoactivated.--

REMARKS

Claims 1-20 have been cancelled and new claims 21-36 have been added. Claims 21-36 are currently pending in the application. All pending claims are set forth in Exhibit B with amendments shown (if applicable).

Attorney for Applicants gratefully acknowledges the interview with the Examiner on 12 July 2002 in which the rejections and the subject matter sought to be covered by the proposed new claims were discussed. The new claims have been submitted to more clearly describe Applicants' invention and to overcome rejections based on 35 U.S.C. 112 second paragraph.

As explained in the interview, the amendments to the specification are for the purpose of expressly incorporating passages from the parent application USSN 09/698,846 that were incorporated by reference in the instant application (page 1, lines 7-8). The passages inserted at page 4, line 10, were amended as indicated in Exhibit A to corrected typographical errors. Further corrections to the figure captions for Figures 4, 33, and 34 have been made to correct typographical errors.

In regard to the new claims, where basis for a term or phrase is found in the incorporated passages, the page and line numbers refer to the location in the parent application 09/698,846. (Such page and line references have the designation "('846)" in the right hand side of the box below).

Basis new claims are as follows:

New Claim(s)	Term/Phrase	Basis
21	"probe set"	Claims 2-20.
21, 30	"$[(D, M)\text{-}L]_k\text{-}T$"	Claim 1 Page 30, line 45.

21, 30	"k ... 1 to 20"	Page 30, line 45. Page 33, Table 4. Page 18, lines 7-8. ('846)
21, 30	"antibody binding compound"	Page 14, lines 27-39. Page 33, Table 4. Page 8, line 15. ('846)
21, 30	"cleavable linkage"	Claim 1 Page 20, line 8, to page 22, line 27. ('846)
21, 30	"distinct charge/mass ratio so that eTag reporters of the plurality of electrophoretic probes form distinct peaks upon electrophoretic separation."	Claim 1 Page 4, lines 21-23. Figs. 5, 6, & 8 Page 8, lines 12-13. ('846) Figs. 7 ('846)
21, 30	"1 to 500 atoms" in reference to M	Page 18, line 6.
21, 31	"group consisting of carbon, hydrogen, oxygen, nitrogen, sulfur, phosphorus, and boron"	Page 18, lines 8-9. Figs. 1C, 5, 6, 15, 17A-J.
22, 31	"1 to 300 atoms" in reference to M	Page 18, line 6.
23	"photolabile"	Page 17, lines 31-32. Page 34, line 37.
24, 32	"cleavable linkages are each an olefin, a thioether, a sulfoxide, or a selenium analog of the thioether or sulfoxide"	Page 19, line 11. ('846) Pages 21-22. ('846)
25	"cleavable by oxidation by singlet oxygen or hydrogen peroxide"	Claims 6 & 7. Page 5, lines 11-13. Page 17, lines 36-37. Page 18, line 16, to page 17, line 3. ('846)
26, 33	"detection group is a fluorophore, a chromophore, or an electrochemical label "	Claim 17.
27, 34, 35	"antibody binding compound is a monoclonal antibody or a polyclonal antibody"	Page 14, lines 27-39.
27, 34	"k is in the range of from 1 to 3"	Page 31, line 5.
28, 33	"distinct charge/mass ratio in the range of from –0.001 to 0.5"	Page 24, line 7-14.
28	"a fluorescein"	Fig. 5
29	"ester linkage"	Page 5, lines 11-13.
29	"esterase"	Page 5, lines 11-13.
30	"reagent pairs"	Page 18, lines 21-22. ('846)
30	"first reagent"	Page 18, lines 21-22. ('846)
30	"second reagent"	Page 18, lines 21-22. ('846)
30	"second antibody binding compound having a sensitizer for generating an active species"	Page 33, Table 4. Claim 37, 38, & 47. ('846) Page 18, line 16, to page 17, line 3. ('846)
30	"active species"	Page 18, line 16, to page 17, line 3. ('846)
35	"active species is singlet oxygen or hydrogen peroxide"	Claims 6 & 7. Page 18, line 16, to page 17, line 3. ('846)
36	"sensitizer is capable of generating singlet oxygen when photoactivated"	Claim 7.

In regard to the above terms, it would be clear to one of ordinary skill in the art that an antibody binding compound may include one or more antibodies or components derived from antibodies,

such as Fab fragments, or the like, or other ancillary components, such as biotins or streptavidin, or like components commonly used in the immunoassay art. Likewise, one of ordinary skill in the art would recognize that the distinctness of an electrophoretic peak could be based on either electrophoretic mobility or fluorescence, as disclosed on page 15, line 28, to page 16, line 2, of parent application 09/698,846.

No new matter has been added by the amendments. Reconsideration is respectfully requested.

Provisional Double Patenting

The Examiner provisionally rejected claims 1-20 under the doctrine of obviousness-type double patenting with respect to the following claims of the following copending applications:

Claims	Ser. No. of Copending Application
1-4	09/824,984
1-10	09/825,247
1-19	09/825,245
1-15	09/825,246
1-10	09/824,905
1-4	09/824,861
1-4	09/824,851

In view of the above amendments, Applicants respectfully disagree with the above rejection as it applies to copending applications 09/825,247; 09/825,245; 09/825,246; and 09/824,905, as the subject matter of these applications is directed to oligonucleotide binding compounds that bind to polynucleotide targets, whereas the subject matter of the present application is directed to antibody binding compounds. Applicants submit that the binding events of the respective methods operate by different mechanisms and that the knowledge of one method by one of ordinary skill in the art would not render the other method and materials obvious.

Applicants have enclosed appropriate Terminal Disclaimers with respect to the above copending applications to overcome the above rejections. Accordingly, Applicants respectfully request that the above rejections be withdrawn.

Rejections Under 35 U.S.C. 112

The Examiner rejected claim 10 under 35 U.S.C. 112 second paragraph because of use of the term "substrate."

Applicants respectfully disagree with this rejection, particularly in view of the above amendments. The above term no longer appears in the pending claims. Accordingly, Applicants request that the rejections by withdrawn.

Rejection Under 35 U.S.C. 102

The Examiner rejected claims 1-2, 8, and 11-20 under 35 U.S.C. 102(b) as being anticipated by Grossman (5,470,705). The Examiner argues that Grossman discloses all the elements of Applicants' composition, including a binding polymer (presumably the rough equivalent of Applicants' "antibody binding compound"), a mobility modifying polymer chain (presumably the rough equivalent of Applicants' "eTag reporter"), and a detection moiety.

Applicants respectfully disagree, particularly in view of the amendments. The binding polymer of Grossman is limited to oligonucleotides or related analogs that bind to a target polynucleotide by hybridization (col. 6, line 56, to col. 7, line 30), and there is no disclosure or suggestion in Grossman of any other class of binding compounds. The "binding" elements of Applicants' composition are "antibody binding compounds" that are not related to oligonucleotides structurally, in the manner in which they are made, or in how they bind to their target compounds. Applicants' "antibody binding compound" element is not disclosed by Grossman. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. 102(b) be withdrawn.

Rejections Under 35 U.S.C. 103

The Examiner rejected claims 5-6 under 35 U.S.C. 103(a) as being unpatentable over Grossman (5,470,705) in view of McGall (5,843,655). The Examiner applies Grossman as described above. McGall discloses a variety of cleavable linkages for use in quality control methods in spatially directed solid phase synthesis of oligonucleotide probes on arrays. The Examiner argues that it would be obvious to one of ordinary skill in the art to combine the probes of Grossman with the cleavable structures of McGall to obtain Applicants' compositions that include non-enzymatically cleaved eTag reporters.

Applicants respectfully disagree, particularly in view of the above amendments. First, to the extent that Grossman discloses cleavage of a bond (Fig. 19A-B; col. 19, line 62, to col. 20, line 44), such cleavage is only with the use of enzymes recognizing nucleic acid substrates having bound probes, e.g. polymerase, exonuclease, and restriction endonucleases. Thus, the enzyme cleaves a probe only when it successfully binds to its target sequence. Unbound probe is not cleaved. Grossman contains no disclosure or suggestion that other types of cleavage may be

possible or desirable. In contrast, McGall discloses cleavage methods that act on all the reaction components throughout the reaction mixture. If a component is capable of cleavage, no matter where it is in the mixture, it will be cleaved. Thus, the only way that a cleavage method of McGall could be combined with the method of Grossman, would be if a wash step were included to remove unbound probe. However, the only wash step proposed in Grossman (Figs. 20A-C; col. 20, line 46, to col. 21, line 15) is for an alternative embodiment to the "nuclease cleavage" embodiment. Thus, Grossman teaches away from direct substitution of the cleavable linkages of McGall.

Second, Grossman's oligonucleotide probes form duplexes by hybridization of complementary nucleotides in the probe and target sequence, that are natural substrates for a variety of nucleases. In contrast, Applicants' probes do not form duplexes or other structures that are natural substrates for an enzyme. Thus, cleavage in Applicants' method requires either a separation step, or a locally acting cleavage agent, or both. The same requirements exist for Grossman, but they are automatically satisfied because his methods are limited to nucleic acid probes and target. Thus, the substitution of McGall's cleavable linkages into Grossman's method, without additional teaching, would not be obvious to one of ordinary skill in the art.

In view of the above, Applicants respectfully request that the rejection under 35 U.S.C. 103(a) be withdrawn.

The Examiner rejected claim 7 under 35 U.S.C. 103(a) as being unpatentable over Grossman in view of Breslow (6,331,530). The Examiner applies Grossman as above. Breslow discloses a compound for cancer therapy consisting of cyclodextrin dimers whose cyclodextrin pairs are connected by a linkage which is cleaved by singlet oxygen generated by photosensitizers. The Examiner argues that, as with the McGall linkages, it would obvious to one of ordinary skill in the art to substitute the singlet oxygen-labile linkage of Breslow into the probes of Grossman to obtain Applicants' invention.

Applicants respectfully disagree, particularly in view of the above amendments. As explained above in regard to McGall, because Grossman's probes and targets are nucleic acids, the substitution of Beslow's linkage into Grossman's probe requires either a locally acting cleavage agent or a wash step prior to application of the cleavage agent. The former is accomplished in Grossman by virtue of using enzymes that recognize or operate on double stranded DNA substrates. However, Beslow's linkage is cleaved by singlet oxygen generated by a photosensitizer in the proximity of the linkage. Note that in Breslow the cyclodextran dimer is a carrier of the photosensitizer (col. 1, lines 52-57; col. 3, lines 45-46; and elsewhere). *Thus, the linkage disclosed*

by Breslow comes with its own local source of singlet oxygen. There is no teaching or suggestion in either Grossman or Breslow, whether alone or together, how this same situation could be achieved with Grossman's probes that use Breslow's linkages without independent invention.

Applicants submit that their probe sets would not be obvious to one of ordinary skill in the art based on Grossman in view of Breslow. Accordingly, Applicants respectfully request that the above rejection be withdrawn.

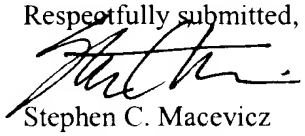
The Examiner rejected claim 9 under 35 U.S.C. 103(a) as being unpatentable over Grossman in view of Cantor (5,849,878). The Examiner applied Grossman as above. Cantor discloses bis-antibody-DNA conjugates (i.e. "antibody-dsDNA-antibody" conjugates) wherein the DNA linkage has a restriction endonuclease recognition site. The Examiner argues that it would be obvious to one of ordinary skill in the art to substitute the antibody-DNA conjugates of Cantor with the probes of Grossman to obtain the compositions of Applicants' claim 9.

Applicants submit that the present rejection has been obviated by the above amendments, as the particular subject matter of claim 9 is not included in the currently pending claims. Accordingly, Applicants respectfully request that the rejection be withdrawn.

In view of the above, Applicants submit that the claims as written fully satisfy the requirements of Title 35 of the U.S. Code, and respectfully request that the rejections thereunder be withdrawn and that the claims be allowed and the application quickly passed to issue.

If any additional time extensions are required, such time extensions are hereby requested. If any additional fees not submitted with this response are required, please take such fees from deposit account **50-2266**.

Respectfully submitted,



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Enclosures:

Terminal Disclaimers for USSNs: 09/824,905; 09/825,245; 09/825,246; 09/825,247; 09/824,851; 09,/824,984; and 09/824,861.
Petition for Time Extension
CPA Request Transmittal form PTO/SB/29
Supplemental Information Disclosure Statement with cited references

Exhibit A
Amendments to the Specification showing Insertions and Deletions

Page 4, line 10, with amendments shown:

--Methods and compounds are provided for multiplexed determinations, where the compounds can be linked to binding compounds for detection of reciprocal binding compounds in a sample. The methods are distinguished by having a plurality of binding events in a single vessel using a mixture of differentially eTag reporter [~~receptor~~] conjugated binding compounds, the release of identifying eTag reporter [~~receptor~~] of those binding compounds bound to their target compounds in the same vessel, and the detection of the released identifying tags by separation of the tags in a single run. The eTag reporter [~~receptor~~] are distinguished by having one or more physical characteristics that allow them to be separated and detected.

The method employs a mixture of binding compounds bound to eTag reporters, where each eTag reporter has a characteristic that allows it to be uniquely detected in a single separation run. The method involves combining the eTag reporter conjugated binding compound with a sample to determine the presence of a plurality of targets under conditions where the binding compounds bind to any reciprocal binding partners to form a binding complex. After sufficient time for binding to occur, the eTag reporters can be released from binding complexes in the same vessel. Various techniques are employed depending upon the nature of the binding compounds for releasing the eTag reporters bound to the complex. The released eTag reporters are then separated and identified by their differentiable characteristics free of interference from the eTag reporters still bound to the binding compound. The techniques for differentiating between eTag reporters bound to a complex and not bound to a complex, include enzymatic reactions that require the complex to exist for cleavage to occur, modification by using ligand/receptor binding, where the ligand is part of the binding compound, so that after cleavage, eTag reporter [~~receptor~~] still bound to the binding compound is modified, dual binding to the target resulting in release of the eTag reporter [~~receptor~~], where optionally eTag reporter [~~receptor~~] bound to the binding compound is modified, and the like.

One set of eTag reporters [~~receptors~~] are distinguished by differences, which include mass as a characteristic. These eTag reporters do not rely on differentiation based on oligonucleotides of 2 or more, usually 3 or more nucleotides, but rather on organic chemical building blocks that are conveniently combined together to provide for large numbers of differentiable compounds. Therefore, while the original eTag reporter or eTag reporter

conjugated to the binding compound can have 2 or more nucleotides, when released from the binding compound, the released eTag reporter will have not more than 3, usually not more than 2 nucleotides. Of particular interest are eTag reporters [~~receptors~~] that are characterized by differences in their mass/charge ratio. These compounds are distinguished by having differences in mobility and are characterized by having regions, which serve as (1) a cleavable linking region; (2) a mass-modifying region; (3) a charge-modifying region: and (4) a detectable region, where the regions may be separate and distinct or combined, there being at least two distinct regions that provide for the differentiation. These eTag reporters may be combined in kits and assays with compounds having all of the regions within a single region to further expand the number of different compounds used as eTag reporters in a multiplexed determination. These compounds find use with other compounds where the different regions are present in the same moiety, for example one to two regions, where the charge-modifying region may also be the detectable region or the mass-modifying region. By having a plurality of compounds that can serve as identifying molecules, mixtures of target compounds can be assayed in a single vessel. By using protocols that result in the release of eTag™ reporters from the binding compound that are identifiable due to differences in mobility, the analysis is greatly simplified, since the eTag reporters will be substantially free of interfering materials and their differences in mobility will allow for accurate detection and quantitation.—

Page 6, lines 9-10, with amendments shown:

--Figure 4 illustrates the design and synthesis of e-tags using [~~a LabCard (Detection: 4.7 cm; 200 V/cm) and~~] standard phosphoramidite coupling chemistry.—

Page 8, lines 16-17, with amendment shown:

--Figure 33 is a schematic diagram of the steps involved in the synthesis of the phosphoroamidite of biotin-deoxycytosine (dC)[~~(Reagent C)~~].—

Page 8, lines 16-17, with amendment shown:

--Figure 34 is a schematic diagram of the steps involved in the synthesis of the phosphoroamidite of biotin-deoxyadenosine (dA)[~~(Reagent D)~~].--

Page 27, lines 13-19, with amendments shown:

-- In one approach, the e-tag probe is constructed sequentially from a single or several monomeric phosphoramidite building blocks (one containing a dye residue), which are chosen to generate tags with unique electrophoretic mobilities based on their mass to charge ratio. The e-tag probe is thus composed of monomeric units of variable charge to mass ratios bridged by phosphate linkers. Figure 4 illustrates the design and synthesis of e-tags using [~~a LabCard (Detection: 4.7 cm; 200 V/cm) and~~] standard phosphoramidite coupling chemistry.[~~)~~.] The separation of e-tags on a LabCard (Figure 5) has been demonstrated.--